IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Attorney Docket No. 2006_1312A
Hiide YOSHINO et al.	:	**Confirmation No. 4646**
Serial No. 10/588,778	:	Group Art Unit 1628
Filed December 3, 2007	:	Examiner Marcos L. Sznaidman
A NOVEL THERAPEUTIC AGENT FOR AMYOTROPHIC LATERAL SCLEROSIS (ALS) OR DISEASES CAUSED BY ALS	:	**Mail Stop: AMENDMENT**

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Takatomo Yoneoka, declare:

That I am a citizen of Japan; and my full post office address is
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That my education and employment history is as follows:

Education:
1994; Master's degree from Gifu Pharmaceutical University, Pharmaceutical Department

Employment:
1994- TOKYO TANABE CO., LTD. (currently, MITSUBISHI TANABE PHARMA CORPORATION)
Current position:
Clinical Leader at Clinical Research Planning and Coordination Department, Development Division, MITSUBISHI TANABE PHARMA CORPORATION

That I am one of the inventors of the present invention and am familiar with the above-identified application, as well as the Office Action dated July 25, 2011.

I declare further that the following statements are true and correct to the best of my knowledge.

(1) Novelty of the present invention

In "I. Open Administration Trials" on page 4 of Yoshino et al, it is described that 30 mg of edaravone was administered once per day for 14 days to amyotrophic lateral sclerosis (ALS) patients (page 5, lines 1-2). It is further described that the drug was administered for 10 days per month to patients who wanted to continue with the drug (page 5, lines 16-19). The period from the completion of the 14 days intravenous drip administration to the initiation of the continued administration of 10 days per month is not disclosed therein.

The outline of the drug administration period and the drug holiday period in "I. Open Administration Trials" of Yoshino et al is as follows.

		Continued administration period				
Drug administration	Drug holiday	Drug administration	Drug holiday	Drug administration	Drug holiday	---
14 days	Unknown	10 days	20(21) days	10 days	20(21) days	---

On the other hand, the method of claim 1 of the present application is characterized in that a combination of a drug administration period of 14 days and a drug holiday period of 14 days is repeated. Therefore, the method of "I. Open Administration Trials" of Yoshino et al is different from the method of the present invention in "the drug holiday period" and "the drug administration period of the continued administration period".

In "II Short-term Placebo Control Double Blind Comparative Trials" on page 11 of Yoshino et al, it is described that 30mg/day of the edaravone or the placebo (saline solution) was administered for 20 days (Monday trough Friday) to the ALS patients (page 12, lines 6-7), and that 30 mg/day of the edaravone was administered to all of the patients for 14 days after the drug holiday period of 2 weeks (14 days) (page 12, lines 22-24).

The outline of the drug administration period and the drug holiday period in "II Short-term Placebo Control Double Blind Comparative Trials" of Yoshino et al is as follows.

edaravone administration group

Drug administration	Drug holiday	Drug administration
20 days (Monday trough Friday) of 4 weeks	14 days (2 weeks)	14 days

Placebo administration group

Drug holiday	Drug holiday	Drug administration
4 weeks	14 days (2 weeks)	14 days

On the other hand, the method of the present application is characterized in that a combination of a drug administration period of 14 days and a drug holiday period of 14 days is repeated. In the method of the edaravone administration group in "II Short-term Placebo Control Double Blind Comparative Trials" of Yoshino et al, the period of the initial drug administration is 4 weeks which is different from 14 days in the present invention. In the method of the placebo administration group in "II Short-term Placebo Control Double Blind Comparative Trials" of Yoshino et al, a combination of a drug administration period and a drug holiday period is not repeated, and the method of placebo administration group is different from the present invention.

As mentioned above, the method of the present invention is different from the methods of Yoshino et al, and is novel against Yoshino et al.

(2) Unobviousness of the present invention

The results of "I. Open Administration Trials" of Yoshino et al are described on page 6, line 21 in "4. Results Thus Far". The course of the ALSFRS-R score of the 23 cases (excluding 12 cases who reached the hard end point within 6 months after the drug was first administered and excluding 7 cases whose follow-up could not be carried out) is shown. The ALSFRS-R score had declined by 6.9 points to 31.3 points when the drug was first administered, from the 38.2 points at 6 months before the drug was administered. The ALSFRS-R score after administration of the drug was started had declined 5.2 points to an average of 26.1 points (see page 7). These results show that edaravone (3-methyl-1-phenyl-2-pyrazolin-2-one) suppressed the decline of the ALSFRS-R score for 6 months by 1.7 points.

On the other hand, the averages of the measured ALSFRS-R scores at 6 months before the drug administration, at the time of the drug administration and at 24 weeks after the drug administration in the edaravone (30mg) administration group in Example 1 of the present application are as follows.

	At 6 months before the drug administration	At the time of the drug administration	At 24 weeks after the drug administration
ALSFRS-R score	39.3	32.0	27.0

In the above table, in order to make the condition consistent with the condition of 23 patients whose ALSFRS-R scores are shown in Yoshino et al, the average of the ALSFRS-R scores of 4 patients among from 5 patients of 30mg edaravone administration group in Example 1 of the present application (excluding 1 patient who reached the hard end point within 6 months after the drug was first administered) is shown.

These results show that the ALSFRS-R score had declined by 7.3 points to 32.0 points when the drug was first administered, from the 39.3 points at 6 months before the drug was administered. The ALSFRS-R score at 24 weeks after administration of the drug was started had declined 5.0 points to an average of 27.0 points. These results show that edaravone (3-methyl-1-phenyl-2-pyrazolin-2-one) suppressed the decline of the ALSFRS-R score for 6 months by 2.3points.

When the suppressive effect of 2.3 points in the present invention is compared with the suppressive effect of 1.7 points in Yoshino et at, the suppressive effect of the present invention is more superior than that of Yoshino et al by 0.6 points. It is reported that 1 point of ALSFRS-R score increases the risk of death or tracheotomy by 7% (Neurology 2005; 64:38-43). Therefore, the 0.6 points difference is considered to decrease the risk of death or tracheotomy by about 4 %, which has very significant meaning for ALS patients. The aforementioned difference of the suppressive effect is considered to arise from the difference of the administration method. Namely, in the present invention, the ratio of the drug administration period (14 days) and the drug holiday period (14 days) is 1:1, while the ratio of the drug administration period (10 days) and the drug holiday period (20 or 21 days) is 1:2 for the continued administration period in Yoshino et al, although the ratio of the drug administration period and the drug holiday period for the initial (first) administration in Yoshino is unknown.

As demonstrated in the Declaration filed on February 3, 2010, a more excellent effect of treating amyotrophic lateral sclerosis (ALS) or symptoms caused by ALS and/or the suppressing the progression thereof, is achieved when a combination of the drug administration period (2 days) and the drug holiday period (2 days) is repeated, as compared with the case when the drug holiday period is not provided. In the present invention, the drug holiday period which is almost the same period as the drug administration period is provided, and a combination of the drug administration period and the drug holiday period is repeated, thus an advantageous effect is achieved. Therefore,

the present invention is not obvious from Yoshino et al.

I further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

October 19, 2011
Date

Takatomo Yoneoka
Signature; Takatomo Yoneoka